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Anodal transcranial direct current stimulation over the ventromedial prefrontal cortex enhances fear extinction in healthy humans: A single blind sham-controlled study

Anxiety disorders are among the most common mental disorders [1,2]. Fear extinction is considered essential to promote successful treatment of several anxiety disorders. Neuroscience research has provided evidence for the contribution of the ventromedial prefrontal cortex (vmPFC) in extinction learning and recall [3,4]. Its role in fear extinction has been investigated via transcranial direct current stimulation (tDCS) in a recent sham-controlled study involving healthy participants. In that study [5], 5 minutes of 2 mA anodal stimulation over the left vmPFC during fear extinction reduced the physiological expression of fear (reduction of Skin conductance response - SCR) induced via Pavlovian conditioning. However, no effects were reported for the recall session.

We extended this study by applying tDCS for 10 minutes over the vmPFC during fear extinction, and hypothesized that this intensified stimulation enhances tDCS efficacy.

Thirty-two participants with an age mean of 24.15 years were recruited from the University of Tasmania by online advertisements. They were randomly assigned to one of two sub-groups: anodal ($n = 16$, 5 males) or sham ($n = 16$, 5 males) stimulation. Participants provided written informed consent; procedures were approved by the local ethics committee.

Separate repeated measures ANOVAs were conducted on participants that acquired (*Anodal* tDCS: N = 12, 5 males, 7 females; *Sham* tDCS: N = 11, 5 males, 6 females), or did not acquire (i.e., SCR for CS- higher than for CS+ in the acquisition session: N = 4, *Anodal*, 4 females; N = 5, *Sham*, 1 male) autonomic signs of fear in response to Pavlovian fear conditioning. Standard tDCS exclusion criteria were applied for participant screening (Supplemental material – SM- for details). The experiment was conducted over two consecutive days, using the same experimental context (time of day, room). For tDCS, rubber electrodes (one anode and one cathode) were covered with saline-soaked sponges (5 × 5 cm). The sponge pocket was saturated with physiological saline solution. The *Anode* was placed over the AF3 position (according to the international 10–20 system) targeting the vmPFC [e.g., 5]. The return electrode was placed over the contralateral mastoid process, as in the former study [5]. Real tDCS (2 mA) was applied for 10 minutes. Skin conductance level was measured through a 22 mV_{rms} 75 Hz constant-voltage coupler (GSR Amp, *ADInstruments*, Australia) with bipolar electrodes positioned over the intermediate phalanges of the first and third finger of the non-dominant hand, sampled at 512 Hz, stored at 64 Hz, and recorded in micro-Siemens (μS). The study employed a standardized differential fear conditioning and extinction task [6]. A colored circle (Conditioned Stimulus - CS) was paired with a 500 ms mild electrical shock (US) inducing a conditioned fear response (CS+) during the acquisition phase, while another colored circle was never paired with the shock (CS-). This was followed by an extinction phase where no shocks were delivered, and the CS + -dependent SCR amplitude was expected to diminish accordingly. On Day 2, participants repeated the extinction phase to determine return of fear. Real or sham tDCS was administered during fear extinction learning. See Fig. 1a for details concerning experimental procedures.

Squared root transformation was applied to raw SCR data to reduce variability in accordance with previous studies [i.e., 5]. For participants that acquired fear, in the *extinction session* the stimulus × group interaction term showed a trendwise effect [$F(1,17)$] = 3.958, $p = 0.062$, $h_p^2 = 0.188$]. A significant difference in SCR between CS+ and CS- emerged for the sham ($p = 0.049$, $M = 1.579$ vs. $M = 1.441$), but not for the anodal group ($p = 0.999$, $M = 1.348$ vs. $M = 1.343$, Tukey post-hoc tests). For the *Recall session*, the Stimulus × group interaction was significant [$F(1,16) = 5.023$, $p = 0.039$, $h_p^2 = 0.238$]. The SCR difference between CS+ ($M = 1.447$, $SEM = 0.057$) and CS- ($M = 1.261$, $SEM = 0.062$) was significant ($p = 0.006$) in the sham tDCS group. No difference ($p = 0.100$) emerged between CS+ ($M = 1.292$, $SEM = 0.051$) and CS- ($M = 1.254$, $SEM = 0.055$) in the Anodal tDCS group (see Fig. 1b). Finally, the group x block x stimulus × trial interaction was significant [$F(4,64) = 2.698$, $p = 0.038$, $h_p^2 = 0.144$]. Post-hoc comparisons showed a significant difference for trial n 5 of the early block of the sham group ($p < 0.05$). No significant results emerged in participants that did not show fear acquisition (see SM for details).

Overall, tDCS over the left vmPFC appears to reduce the sympathetic component of fear reactions in extinction in participants that acquired fear responses during fear acquisition. In the *Sham* group, participants show higher SCR for CS + trials, as compared to CS- trials, in both, the extinction and recall sessions. This suggests that in the *Sham* group CS + trials continued to be perceived as a threat. By contrast, no SCR difference was detected between CS+ and CS- trials in the *Anodal* group during the recall session, and trendwise in the extinction learning session, in line with [5]. Therefore, tDCS had a facilitatory effect on consolidation of extinction, as compared to initial extinction learning.

Abbreviations: **PTSD**, Post-traumatic Stress Disorder; **vmPFC**, Ventro-Medial Prefrontal Cortex; **tDCS**, Transcranial Direct Current Stimulation; **SCR**, Skin Conductance Response; **SEM**, Standard Error Mean.

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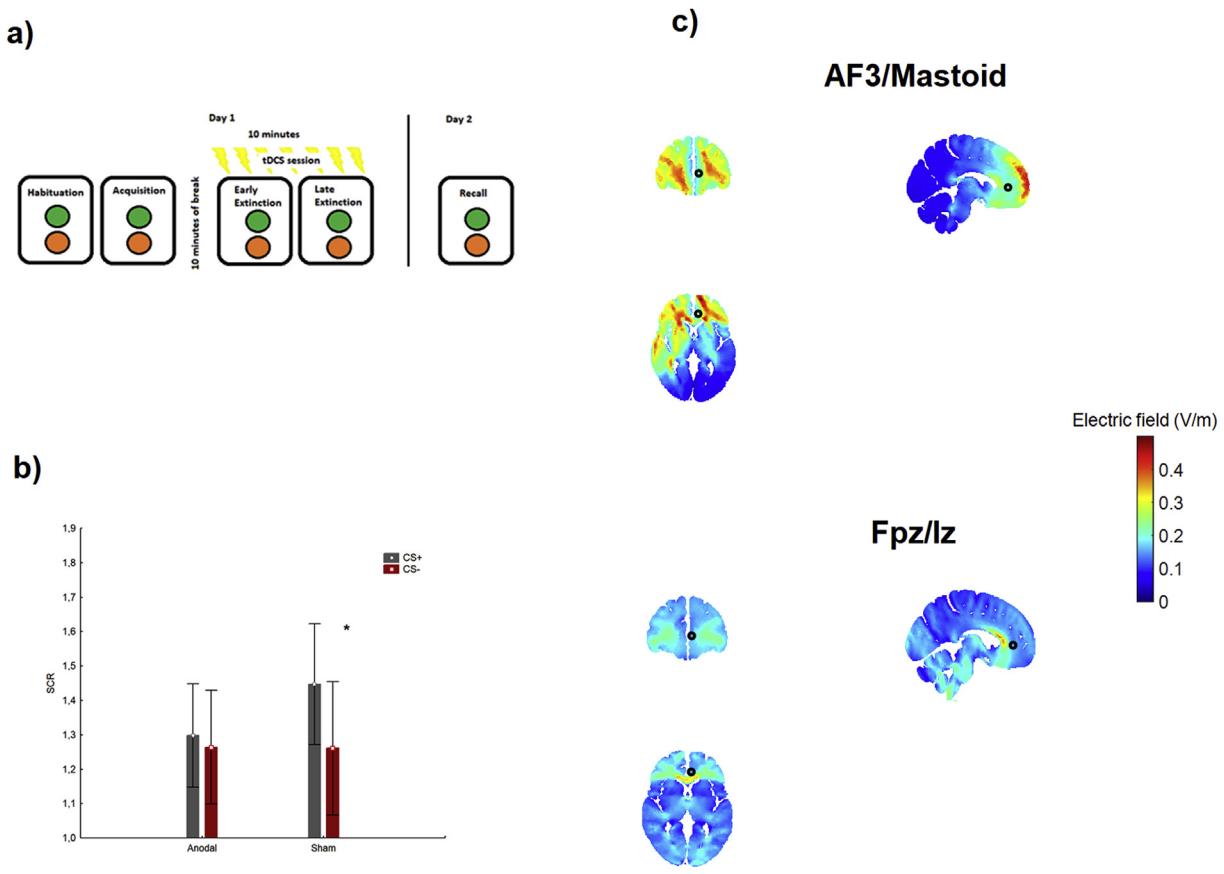

Fig. 1. **a)** Overview of the experimental procedures, including timing of tDCS (i.e., during extinction learning blocks). Colored circles represent CS+ and CS- stimuli; **b)** SCR mean for Anodal and Sham groups in the recall session (i.e., early, late) during the exposure to CS+ and CS- stimuli. The results show a significant difference between CS- and CS + only for the sham group; * indicates significant difference. Vertical bars denote ± standard errors (more details are provided in SM); **c)** The figure shows results of electrical field simulation with electrode positions based on previous studies with positive [5] and negative [7] results on fear extinction learning. Current flow is associated with placement (top figure) of the target electrode over **AF3** (return electrode placed over the contralateral mastoid) and (bottom figure) over **FPz** cortical target (return electrode over the occipital lobe). The results for **AF3** shows stronger electrical fields at the level of the amygdala, and vmPFC, which are strongly involved in fear extinction [3], compared to **FPz** results.

In conclusion, our results corroborate and also extend those provided by van 't Wout et al. [5], as we showed that prolonged tDCS, as compared to the former protocol, facilitates fear extinction consolidation.

In another study [7], which applied 1.5 mA anodal tDCS for 20 minutes over the mPFC during fear extinction, the authors reported however a generalization of fear expression to the neutral stimulus in the respective recall session. Substantial differences in the adopted protocol such as the paradigm to induce fear conditioning, number of trials, stimulation parameters, including electrode size, position of the anodal target and the return electrodes, and the position of the target electrode over FPz instead of AF3 might explain outcome differences, as compared to the results of the present study, and those reported by van 't Wout et al. [5]. According to our modeling results (Fig. 1 c), the latter [7] might have resulted in less activation of the vmPFC, and amygdala, which are both crucial for extinction learning [e.g., 3], compared to Ref. [5].

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Declaration of competing interest

M.A.N is on the Scientific Advisory Boards of Neuroelectrics, and Neurodevice. There are no other conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.12.022.

References

[1] Hofmann SG. Cognitive processes during fear acquisition and extinction in animals and humans: implications for exposure therapy of anxiety disorders. Clin Psychol Rev 2008;28:199–210.
[2] Vicario CM, Salehinejad MA, Felmingham K, Martino G, Nitsche MA. A systematic review on the therapeutic effectiveness of non-invasive brain stimulation for the treatment of anxiety disorders. Neurosci Biobehav Rev 2019;96:219–31.
[3] Phelps EA, Delgado MR, Nearing KI, LeDoux JE. Extinction learning in humans: role of the amygdala and vmPFC. Neuron 2004;43(6):897–905.
[4] Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am J Psychiatry 2007;164(10):1476–88.
[5] van 't Wout M, Mariano TY, Garnaat SL, Reddy MK, Rasmussen SA, Greenberg BD. Can transcranial direct current stimulation augment extinction of conditioned fear? Brain Stim 2016;9:529–36. 2016.
[6] Orr SP, Metzger LJ, Lasko NB, Macklin ML, Peri T, Pitman RK. De novo conditioning in trauma-exposed individuals with and without posttraumatic stress disorder. J Abnorm Psychol 2000;109(2):290–8.

[7] Abend R, Jalon I, Gurevitch G, Sar-El R, Shechner T, Pine DS, Hendler T, Bar-Haim Y. Modulation of fear extinction processes using transcranial electrical stimulation. Transl Psychiatry 2016;6(10):e913.

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